Office Action Summary	Application No.	Applicant(s)
	10/590,829	STROBEL ET AL.
	Examiner	Art Unit
	JENNIFER GRASER	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,12-15 and 18-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,12-15 and 18-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☐ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted on 4/6/11/ is made. Claims 1, 12-15 and 18-20 are currently under examination.

a nonelected invention.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1, 12-15 and 18-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it is unclear which at least two mutations would work synergistically to bring the desired result. Additionally, the claims allow for both a) and b) without either c) and d) [or c) and d) without a) and b)]and these are somewhat duplicative mutations. Alternatively, it could be read that the two mutations are recited separately in A), B), C) and D). The claims also recite the overexpression of "homologous proteins of MutL or MutS" and the metes and bounds of this term cannot be understood. What structure falls under the category of 'homologous"? Appropriate clarification and/or correction is requested.

The mere recitation of a name, i.e., MutL or MutS, to describe the invention is not sufficient to satisfy the Statute's requirement of adequately describing and setting forth

the inventive concept. The claim should provide any structural properties, such as the amino acid sequence of the protein or the nucleic acid sequence of the gene, which would allow for one to identify the protein without ambiguity. The mere recitation of a name does not adequately define the claimed protein. There is no structure recited for *either* the mutations or the DNA repair mechanisms. The description of the invention is not sufficient to satisfy the Statute's requirement of adequately describing and setting forth the inventive concept. The claim should provide any structural properties, such as the location of the mutations and the nucleic acid sequence which is to be mutated and the specific repair mechanisms, which would allow for one to identify the reagents without ambiguity. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. Appropriate correction and clarification is requested.

Claim Rejections - 35 USC § 112-Written Description

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 12-15 and 18-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In 1999, the United States Patent and Trademark Office ("USPTO") published training materials regarding the examination of patent applications under the written description requirement of 35 U.S.C. § 112, first paragraph. (See http ://www.uspto. gov/web/offices/pac/writtende sc.pdf). Since that time, the case law and technology have developed in such a way as to necessitate a revision of the 1999 training materials. Consequently, this 2008 revision was created to supersede and replace the 1999 training materials. To the extent that any conflict exists between the 1999 training materials and the present materials, the present materials control. The claims have been evaluated with regard to written description based on the Written Description Guidelines and Training Materials published in 2008/

The instant claims are broadly drawn to a "process for reducing the spontaneous mutation frequencies in a cell or an organism by introducing at least two mutations, whose combined actions lead to at least two enhanced cellular DNA repair". The claims comprise introducing into E.coli an antimutator allele of a gene encoding DNA polypermase IV and/or an antimutator of a gene encoding any sub-unit of DNA polymerase III. Overexpression of any **homologous** protein of MutL or MutS is also disclosed, yet it is unclear which structures are encompassed by this term. There are no 'MutL' or MutS homologs instantly discosed.

There is no structure recited for either the mutations or the DNA repair mechanisms. What are the mutations and do they need to be in a certain order to provide the desired result? The instant specification has only taught a process for mutating the bacteria, E.coli, and the genes involved are: the overexpression of MutL (involved in mismatch repair) and MutS reduce spontaneous mutations of wild-type E.coli cells dramatically and this is in a synergistic manner and also lead to enhanced E.coli cell viability; antimutators dinB10 and dnaE911 reduce the spontaneous mutation by the deletion of MutS. The mutations which possess written description are in E.coli only and include at least two mutations selected from:

A mutation leading to an up-regulation of the expression of the MutL protein;

A mutation leading to an up-regulation of the expression of the MutS protein;

Introduction of antimutator allele dinB10 (to the cell; and,

And introduction of antimutator allele dnaE911 (a gene encoding a subunit of DNA polymerase III).

The specification does not provide written description for any other methods, e.g., use of other cells or organism or any other mutations. Written description is not provided for homologous proteins of MutS, MutL or DNA polymerase IV or III.

Additionally, the claims allow for both a) and b) without either c) and d) [or c) and d) without a) and b)]and these are somewhat duplicative mutations. The specification has not shown results with these different combinations of mutations.

To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. Applicants have not described the genus of claimed nucleotides such that the specification might reasonably convey to the skilled artisan that Applicants had possession of the claimed invention at the time the application was filed.

The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112,

paragraph 1, "'Written Description" Requirement (66 FR 1099-1111, January 5,2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed. The Guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus'" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Absent a detailed and particular description of a representative number, or at least a substantial

number of the members of the genus of ***any*** cell or organism and any mutations which have an effect on enhancing ***any*** cellular DNA repair mechanism, the skilled artisan could not immediately recognize that Applicants were in possession of the claimed genus of peptides at the time of filing. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus, and thus, that the applicant was not in possession of the claimed genus. The claimed subject matter is not supported by an adequate written description because a representative number of species has not been described. There are no drawings or structural formulas disclosed of any of these other possible mutations to other possible organisms and cells.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect additional mutations in E.coli or mutations in any other organism or cell 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). With regard to (4) the

nature of the invention and (5) the state of the prior art, these have been discussed above. One of skill in the art would require guidance, in order to practice the methods as instantly claimed.

Response to Applicant's arguments:

Applicants argue that their amendments to the claims obviate this rejection. This has been fully and carefully considered but is not deemed persuasive. They have not addressed the lack of written description regarding "homologous proteins of MutL or MutS", nor have they addressed the lack of specific nucleic acid/sequence information in the instant claims.

Claim Rejections - 35 USC § 112-Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 12-15 and 18-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are broadly drawn to a "process for reducing the spontaneous mutation frequencies in a cell or an organism by introducing at least two mutations, whose combined actions lead to at least two enhanced cellular DNA repair". ". The claims comprise introducing into E.coli an antimutator allele of a gene encoding DNA

polypermase IV and/or an antimutator of a gene encoding any sub-unit of DNA polymerase III. Overexpression of **any homologous** protein of MutL or MutS is also disclosed, yet it is unclear which structures are encompassed by this term. There are no 'MutL' or MutS homologs instantly discosed.

There is no structure recited for *either* the mutations or the DNA repair mechanisms. What are the mutations and do they need to be in a certain order to provide the desired result? The instant specification has only taught a process for mutating the bacteria, E.coli, and the genes involved are: the overexpression of MutL (involved in mismatch repair) and MutS reduce spontaneous mutations of wild-type E.coli cells dramatically and this is in a synergistic manner and also lead to enhanced E.coli cell viability; antimutators dinB10 and dnaE911 reduce the spontaneous mutation by the deletion of MutS. The mutations which possess written description are in E.coli only and include at least two mutations selected from:

A mutation leading to an up-regulation of the expression of the MutL protein;

A mutation leading to an up-regulation of the expression of the MutS protein;

Introduction of antimutator allele dinB10 (to the cell; and,

And introduction of antimutator allele dnaE911 (a gene encoding a subunit of DNA polymerase III).

The specification does not provide enablement for any other methods, e.g., use of other cells or organism or any other mutations. Additionally, the claims allow for both a) and b) without either c) and d) [or c) and d) without a) and b)]and these are

somewhat duplicative mutations. The specification has not shown results with these different combinations of mutations.

The specification provides no results or direction for homologous sequences of E.coli MutS, MutL or DNA polymerase IV or III. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. Selective point mutation to one key residue could eliminate the function of the polypeptide. It could eliminate its functional properties. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection/function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes, as instantly claimed, in an antigenic determinant could again result in loss of function. Applicants have provided no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different amino substitutions and the nature and extent of the changes that can be made.

Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for

vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect additional mutations in E.coli or mutations in any other organism or cell 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). With regard to (4) the nature of the invention and (5) the state of the prior art, these have been discussed

above. One of skill in the art would require guidance, in order to practice the methods as instantly claimed.

Given the lack of guidance contained in the specification, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Response to Applicant's arguments:

Applicants argue that their amendments to the claims obviate this rejection. This has been fully and carefully considered but is not deemed persuasive. They have not addressed the lack of enablement regarding "homologous proteins of MutL or MutS", nor have they addressed the lack of specific nucleic acid/sequence information in the instant claims. They have also not addressed the new problem of the instant claims allowing for the two mutations to be both a) and b) without either c) and d) [or c) and d) without a) and b)]and these are somewhat duplicative mutations. The specification has not shown results with these different combinations of mutations.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-15 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al (PNSA. 92: 7951-7955. 1995) and Jingyong et al (J.Bacteriol. 2000. 182(17): 5025-5028).

Jingyong et al teach that overexpression of MutS, and to a lesser extent MutL, in E.coli by transversion mutation can reduce GC-TA mutation. See abstract and column 2, first paragraph on page 5025. Foster et al teach that the presence of a Pol III antimutator allele (dnaE915) reduced adaptive mutations in both polB+ E.coli cells and E.coli cells deleted for polB to below the wild-type level. See page 7951. Foster et al also teach that in previous studies it was shown that a Pol II deletion resulted in a 3-fold increase in adaptive reversion of an episomal frameshift mutation, lacI33::lacZ.

The prior art references have demonstrated that spontaneous mutation frequencies may be reduced in E.coli by several different mutations or antimutator alleles. It would have been prima facie obvious to one of ordinary skill in the art to make any or all of the mutations in an E.coli cell in order to enhance cellular DNA repair mechanisms. One of ordinary skill in the art would have the reasonable expectation that use of more than one mutation to reduce spontaneous mutations would exponentially increase the overall cellular DNA repair mechanisms in a particular cell. Jingyong specifically teaches mutations which included over-expression of both MutS and MutL and, therefore, would inherently increase cell viability.

Response to Applicant's arguments:

Applicants argue that their amendments to the claims obviate this rejection. This has been fully and carefully considered but is not deemed persuasive. The prior art references have demonstrated that spontaneous mutation frequencies may be reduced in E.coli by several different mutations or antimutator alleles. It would have been prima facie obvious to one of ordinary skill in the art to make any or all of the

mutations in an E.coli cell in order to enhance cellular DNA repair mechanisms. One of ordinary skill in the art would have the reasonable expectation that use of more than one mutation to reduce spontaneous mutations would exponentially increase the overall cellular DNA repair mechanisms in a particular cell. Jingyong specifically teaches mutations which included over-expression of both MutS and MutL and, therefore, would inherently increase cell viability.

The instant claims do not recite solely the way the two mutations are introduced in order to reduce mutation frequency, rather they allow for multiple combinations. The prior art already teaches (Jingyong et al) that overexpression of MutS, and to a lesser extent MutL, in E.coli by transversion mutation can reduce GC-TA mutation. See abstract and column 2, first paragraph on page 5025. Foster et al teach that the presence of a Pol III antimutator allele (dnaE915) reduced adaptive mutations in both polB+ E.coli cells and E.coli cells deleted for polB to below the wild-type level. The use of the specific alleles dinB10 and dnaE911 would have been obvious design choices as they are functional equivalents which were well known in the prior art at the time the invention was made.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 8:00 AM-6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645

6/17/11